REMARKS

Claims 23, 28, 30-32, 34-38, 41-43, 61, 66-77, and 79-90 are pending and under examination.

Rejection of Claims under 35 U.S.C. §112, 1st paragraph (Enablement) is Traversed

The Office rejected claims 23, 28, 30-32, 34-38, 41-43, 61, 66-77, and 79-90 as allegedly lacking enablement. Office Action at pages 2-7. Based on the following remarks, the rejection is traversed.

In addition to the arguments presented in Applicants' previous replies, Applicants wish to again expressly note the Office's comment regarding the references cited in support of the enablement rejection:

> [The references] accurately reflect the unpredictability in the art of gene therapy that remains today, and the success of a particular oligonucleotide to provide in vivo affects does not necessarily provide assurance for *clinical* success for a different effector molecule (e.g., an inhibitory oligonucleotide) to successfully target a different target gene or to exert its effects predictably in an organism.
>
> One is not necessarily able to extrapolate the success in one *clinical* situation to another situation, especially where different effector molecules are used to target different genes of interest, or are involved in different biochemical mechanisms

Office Action at page 5, lines 7-14; Quotations in original; Emphasis added. The Office then states that:

> Meyer [of record] at page 546 [ ] discloses the unpredictability of this field, where Exon 7 of the SMN2 gene is one of the best studied exons of the human genome, yet many hurdles still exist in achieving *clinical* efficacy: ..."the oligonucleotides did not reach the spinal cord, and hence no therapeutic benefit could be demonstrated ..."
>
> See also Marquis [of record] at page 1479, last full paragraph, pointing out the ongoing delivery obstacles that must be overcome in gene therapy: "However, it is unclear whether such oligonucleotides can be delivered to motoneurons, a treatment which would have to be repeated frequently."

Office Action at page 5, lines 7-14; Quotations in original; Emphasis added.

From the passages quoted above, it appears that the Office is of the opinion that the claimed invention will not be enabled until it is *clinically* available. However, this is not the proper legal standard to be applied.

As explained in *In re Brana*, 51 F.3d 1560, 1567, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995), the USPTO should not confuse "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption," citing *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994). Nonetheless, at page 6, lines 14-18 of the Office Action, the Office maintains that:

> Other experimentation required to practice the invention claimed includes determining accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues in an organism, whereby the compound or compounds are effectively delivered in adequate quantities to the target cells.

But determining accessible target sites on a target RNA molecule is standard for any method involving annealing of polynucleotides, and is routine for the person of ordinary skill in the art. With regard to showing efficacy in delivery and formulations for targeting oligonucleotides to appropriate cells and/or tissues, the evidence of record shows that not only is this possible, the oligonucleotide thus delivered had a beneficial effect *in vivo* in a wide range of tissues using a range of different delivery modes. Even if the optimal mode of delivery/formulation has to be determined for individual specific indications before clinical approval can be obtained, this would not detract from the enablement of the claims.

As additional evidence for enablement, Applicants submit herewith as exhibit a copy of a recent article by Hua *et al.* entitled "Antisense correction of SMN2 splicing in the CNS rescues necrosis in a type III spinal muscular atrophy (SMA) mouse model," Genes Dev., 24: 1634-1644 originally published online July 12, 2010 ("Hua"). According to Hua, it is possible to inject oligonucleotides into the central nervous system (CNS) and see a beneficial effect on the SMA model mouse *in vivo*. This is very simple, and there was no technological problem preventing a person of ordinary skill in the art from doing the same for the present invention. The method of the present invention would be expected to work as well (or better) if oligonucleotides as defined in the claims of the present application were administered in the same way.

The Office's contention appears to express concerns regarding possible problems which may have to be overcome in order for the claimed invention to be useful in a *clinical* setting. In reviewing the reasoning and facts relied on by the Office, the Office's position regarding alleged lack of enablement appears premised upon the possibility that some of the specific protocols described in the references may not be approved for *clinical* use. Indeed, a number of the

Office's assertions as well as the quotes relied upon by the Office from the references refer to problems or obstacles in delivering the therapeutic to the target in a *clinical* setting. However, as stated in *Brana*, that is not the standard for enablement.

Moreover, for the record, Applicants' wish to point out that the Office's comments at page 4, lines 3-11 as they relate to the Specification are in error. It appears that the Office refers to success with the 5' GAA oligonucleotide but not the 5' GGA oligonucleotide. But this is incorrect – the 5' GGA was successful; the 5' GAA was not, which may explain why the Office discusses Tra2 (which binds the GAA oligonucleotide) throughout the Office Action, although the claimed method does not use it.

Absent a fact-based statement from the Office which focuses on the claimed subject matter instead of gene therapy as a general field, Applicants maintain that the Office has failed to establish that the claimed invention is non-enabled. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection.

Rejection of Claims under 35 U.S.C. §103(a) is Traversed

The Office rejected claims 23, 28, 30-32, 34-38, 41-43, 61, 66-69, 71-77, 79, 81, and 86-90 as allegedly obvious over Carlo *et al.* (Molec. & Cell. Biol., Vol. 20, No. 11, pages 3988-3995, 2000) ("Carlo"), Tohyama *et al.* (USPN 7,364,847) ("Tohyama"), and Mitchell *et al.* (US 2004/0126774) ("Mitchell II"), the combination in view of Hofmann *et al.* (Proc. Natl. Acad. Sci., Vol. 97, No. 17, pages 9618-9623, 2000) ("Hofmann"), Lim *et al.* (J. Biol. Chem., Vol. 276, No. 48, pages 45476-45483, 2001) ("Lim"), and Lorson *et al.* (Proc. Natl. Acad. Sci., Vol. 96, pages 6307-6311, 1999) ("Lorson"). In view of the following remarks, the rejection is traversed.

Firstly, Applicants respectfully point out that the Office's reliance on Tohyama as prior art is in error. Tohyama's corresponding WIPO publication of the international application (*i.e.*, PCT/JP02/06462) is not in the English language, therefore, Tohyama does not have a "102(e)" date. Thus, in determining whether Tohyama is prior art, one must consider Tohyama's publication or grant date. Accordingly, the Office's reliance on Tohyama as prior art is incorrect at least because Tohyama was not published or granted before August 16, 2002, which is the filing date of Applicants' foreign priority application, namely United Kindgom Application No. 0219143.5.

In addition to the arguments presented in Applicants' previous replies, Applicants wish to expressly note the Office's comments regarding the newly cited primary reference, namely Carlo:

> It would have been obvious to recruit RNA splicing factors to a target RNA species as instantly claimed to enhance cis-splicing because the general phenomenon of enhancing splicing by bringing the necessary splicing components within close proximity to each other, and to a splicing site were well known in the art as taught previously by Carlo, where binding partners were exploited to bring the necessary factors together to enhance exon slicing.

Office Action at page 11, lines 3-8. The Office then states that:

> It would have been obvious to utilize complementary sequences of known splicing factors as a means of localizing required factors because it was well known in the art that nucleic acids bind to their complementary sequences.

Office Action at page 11, lines 8-11.

Although the U.S. Supreme Court in *KSR v. Teleflex* rejected a "rigid approach" to the application of the recognized Teaching-Suggestion-Motivation test, the Court stated that there still must be some "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR International Co. v. Teleflex Inc.,* 127 S.Ct 1727, 1741, 82 USPQ2d 1385, 1396 (2007) *(quoting In re Kahn,* 441 F.3d 977, 78 USPQ2d 1329 (Fed. Cir. 2006)).

In evaluating the scope and content of the prior art, the Office's "rational underpinning" in support of the Office's assertion of *prima facie* obviousness appears to ignore common knowledge, or common understanding of the person of ordinary skill in the art at the time of the invention. Nothwithstanding the Office's reliance on numerous references that relate to the field of splicing, not a single reference relied-on by the Office teaches or suggests any method that involves employing an *enhancer sequence* to effect splicing in *trans* (*i.e.,* the *enhancer* is *acting* in *trans*). Although a myriad of references may be associated with various discussions relating to splicing, the knowledge in the art available to a skilled worker at the time of the invention neither taught nor suggested the claimed method. The claimed invention provides a relatively simple solution to various problems associated with past attempts for correcting splicing. The simplicity of the claimed inventions, however, does not indicate any lack of non-obviousness.

With respect to Carlo, the reference simply illustrates that a protein binds to a site in the target RNA and speculates that this brings together components at both ends of the exon. But one

of ordinary skill in the art knows that all splicing reactions involve interactions among splicing factors that bring distant parts of the pre-mRNA into proximity; that is what splicing does. It does not recruit to the RNA something that would not naturally bind there; and above all, there is nothing in Carlo about a bifunctional trans-RNA mediating binding to the target. U2AF65, SF1 and U1 snRNP bind to the RNA directly.

The relied-on references do not teach or suggest recruiting a splicing factor to RNA where it would not normally bind, and especially not by using a nucleic acid molecule as required by the claims. There is nothing in any of the relied-on references, in any combination, that teaches that a splicing factor can be recruited by an oligonucleotide to a specific target site on a separate RNA molecule to enhance splicing of the endogenous pre-mRNA.

As previsouly noted, the references relied-on by the Office discuss both normal splicing in which the pre-mRNA to be spliced binds to splicing factors (*e.g.*, Carlo), and trans-splicing in which an exogenous RNA is used as a participant in the splicing reaction (*e.g.*, Mitchell II). But the claimed invention is altogether different, involving a nucleic acid molecule that provides for recruiting a splicing factor to a target RNA where it would *NOT* normally bind. This is a completely distinct invention from the teachings of the relied-on reference that can not be reached by any combination of the cited documents. As evidenced by the record, many laboratories were working on splicing mechanisms at the time of the invention, but only the present inventor had the idea of using bifunctional oligonucleotides to recruit splicing factors. Further, as previsouly noted, the claimed invention was recognized by the RNA community as exciting, important and unique.

For at least the foregoing reasons, no combination of Carlo, Mitchell II, Hofmann, Lim, and Lorson would have rendered Applicants' invention as presently claimed obvious to one of ordinary skill in the art. Moreover, as previously noted, the additional secondary references relied-on by the Office, namely Mitchell II, Hofmann, Lim, and Lorson, are not set forth as curing the noted deficiencies of Carlo as discussed above and for reasons of record. It is believed that none of the secondary references cure the noted deficiencies of Carlo as noted herein.

Accordingly, a *prima facie* case of obviousness has not been established, therefore, the rejection must be withdrawn.

CONCLUSION

Applicants believe the claims are in condition for allowance/issuance and such action is respectfully requested. If issues may be resolved through Examiner's Amendment, or clarified in any manner, a call to the undersigned attorney is respectfully requested.

Respectfully submitted,

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